Research Paper

The Effects of High-intensity Interval Training and Moderate-intensity Continuous Training on Autophagy, Cardiac Remodeling, and Heart Function in Aged Male Rats

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Aging, Cardiac output, Echocardiography, High-intensity interval training (HIIT), Moderate-intensity continuous training (MICT), *mTORC1*, *Atg16*, *Atg7*, *COLIII*, Left ventricular end-diastolic diameter (LVEDD), Left ventricular end-systolic diameter (LVESD), Ejection fraction (EF), Fractional shortening (FS)

ABSTRACT

Introduction: Aging is a physiological process that affects heart function. Training is known as a factor accelerating heart output, especially in aged individuals. In the present experimental study, the authors aimed to evaluate how high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) affect autophagy, cardiac remodeling, and cardiac function.

Methods: Twenty-four male Wistar rats, approximately 20 months old, were divided into three groups of control, HIIT, and MICT. The training programs lasted for eight weeks. Aerobic power and training capacity were also assessed. Two-dimensional echocardiography was also applied to assess cardiac indices. At the end of the experiment, tissue sampling of cardiac tissue was applied, and gene expression was assessed using the qRT-PCR technique. Data were analyzed using SPSS software, version 19.

Results: After HIIT and MICT, no significant changes were detected regarding the animal weight. Also, *mTORC1*, *Atg16*, and *Atg7* gene expression and ejection fraction (EF) and fractional shortening (FS) were accelerated in HIIT and MICT groups compared to control animals. Besides, the collagen type 3 (*COLIII*) gene expression, left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) showed a significant increase ($P<0.05$) in HIIT and MICT animals than control.

Conclusion: Training can potentially improve cardiac output in older adults. Besides, HIIT seems more effective than MICT.

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Introduction

The cardiovascular system undergoes physiological changes with the increase of age, affecting cardiac function. One of the most notable effects is the gradual decline in the heart's ability to pump blood efficiently, known as age-related diastolic dysfunction. This occurs due to the alterations in the structure and function of cardiac muscles and associated connective tissues. These changes can lead to decreased ventricular compliance, impairing the heart's ability to relax and fill with blood during diastole [1]. Additionally, the conduction system of the heart may experience age-related changes, which can lead to arrhythmias and altered heart rate control. The accumulation of oxidative stress and inflammation over time can further exacerbate these effects, potentially contributing to the onset of cardiovascular conditions like heart failure and hypertension in older individuals [2]. Regular exercise, a heart-healthy diet, and appropriate medical management can play crucial roles in mitigating the impact of aging on cardiac function. High-intensity interval training (HIIT) is a form of exercise characterized by brief, intense bursts of activity alternated with rest periods or low-intensity exercise.

It seems that HIIT can effectively improve the cardiovascular system. HIIT is also a time-efficient workout option, as it can be completed in 10-30 min [3]. Moderate-intensity continuous training (MICT) also involves maintaining a steady pace of moderate intensity for a prolonged period. MICT has been shown to improve cardiovascular health, increase endurance, and aid in weight loss [4]. The mammalian target of rapamycin complex 1 (mTORC1) is involved in several cellular functions such as protein synthesis, autophagy, and metabolism.

In the heart, mTORC1 is essential for controlling cardiac function and growth. Activation of *mTORC1* in cardiac myocytes promotes protein synthesis and hypertrophy, which can lead to cardiac dysfunction and heart failure. Additionally, *mTORC1* is involved in regulating mitochondrial function and energy metabolism in the heart. Dysregulation of *mTORC1* signaling has been linked to different heart conditions, such as ischemia-reperfusion injury, cardiomyopathy, and heart failure [5]. *Atg16* is a key regulator of autophagy, a process where cells dismantle and reuse damaged or unneeded parts. Autophagy is crucial for maintaining heart function and protecting against various stressors. Research indicates that *Atg16* expression increases in response to cardiac stress, including ischemia-reperfusion injury or pressure overload. This upregulation of *Atg16* promotes autophagy and protects against cardiac dysfunction and heart failure. Conversely, downregulation of *Atg16* has been linked to impaired autophagy and increased susceptibility to cardiac injury [6]. *Atg7* is another essential gene involved in the regulation of autophagy. Like *Atg16*, *Atg7* expression is upregulated in response to cardiac stress and plays a crucial role in safeguarding against cardiovascular conditions. Studies have shown that *Atg7* deficiency in the heart leads to impaired autophagy and increased susceptibility to cardiac injury [7]. The collagen type 3 (*COLIII*) gene is known to play a crucial role in the maintenance of cardiac function. Collagen is a structural protein that provides support and elasticity to the heart tissue. Decreased expression of *COLIII* has been linked to impaired cardiac contractility, while increased expression has been associated with fibrosis and stiffening of the heart muscle [8]. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), ejection fraction (EF), and fractional shortening (FS) are important cardiac indices that are used to assess cardiac function. LVEDD and LVESD measure the size of the left ventricle at the end of diastole and systole, respectively, indicating the level of chamber dilation or hypertrophy. EF measures the percentage of blood ejected from the left ventricle, while FS is the percentage of changes in the left ventricle's diameter during systole compared to diastole. Together, these indices provide valuable information about the contractile function of the heart and can help diagnose and monitor various cardiac diseases, such as heart failure, myocardial infarction, and cardiomyopathy [9].

According to the abovementioned explanations, the authors aimed to assess the impact of HIIT and MICT on improving heart function by examining gene pathways of *mTORC1*, autophagy (*Atg16* and *Atg7*), collagen disposition (*COLIII*), and cardiac function indicators (LVEDD, LVESD, EF, and FS).

Materials and Methods

Animal preparation and ethical consideration

This experimental investigation was conducted on 24 old (≈20 months) Wistar male rats with an average weight of 350±50 g (obtained from Pasteur Institute, Tehran, Iran). The research animals included three groups of control, MICT, and HIIT. The prepared animals were transferred to the laboratory of Iran University of Medical Sciences. All stages of animal manipulation and ethical issues were conducted according to the guidelines set forth by the ethics committee for conducting research with laboratory animals. The animals were housed in-

dividually in transparent polyethylene cages. Standard conditions for laboratory animals were prepared as 23-25 °C, 45-50% humidity, and 12 light/12 dark photocycle. Free access to standard pellets and water is also provided. The animals' weights were fully documented before the experiment and tissue sampling [10].

Training protocols of HIIT and MICT

The training groups were organized into two groups of HIIT and MICT. Besides, the control group received no training. Treadmilling was set at a slow speed of 3 m/min. Each group performed the associated protocol five days per week (for eight weeks). On the sixth day, the maximum oxygen consumption (VO_2max) was measured. The day of seven was also defined for animal recovery [11]. MICT protocol included 5 min of body warming-up with the intensity of 30-40% VO_2max, 30 min of running with the intensity of 60-65% VO_2max, and 5 min of body cooling-down with the intensity of 30-40% VO_2max. The HIIT protocol consisted of 30 min of running on a treadmill with eight different intervals in each session, which included (a) five minutes of warming-up at an intensity of 30-40% VO_2max, (b) three minutes at an intensity of 85-90% VO_2max with two minutes of rest at an intensity of 30-35% VO_2max between each interval. In the first weeks, the intense intervals were applied at 85% VO_2max; (c) five minutes of cooling-down at an intensity of 30-40% VO_2max. The training intensity for each week was adjusted and determined based on running speed, and the training intensity increased by 0.02 m/s every week [12].

Aerobic power and training capacity assessment

The training capacity test was performed in two stages, each for two days, before the main training program and at the end of each week. After three minutes of body warming-up (5 m/min), the treadmill speed was increased to 4 m/min every two minutes. The maximum speed was defined when the rats could not run at a constant speed for at least 90 seconds (treadmill incline was 0 °). According to the published studies, the maximum speed with a lactate concentration >6 mMOL/L and breathing ratio of VCO_2/VO_2 was equal to 1.5 [12].

Two-dimensional echocardiography

24 h after the last training, two-dimensional (2D) chest-connected echocardiography was performed (M-mode model, GE-VIVID-7, V.5, USA) equipped with the 10 MHz transducer. Following anesthesia induction using IP injection of sodium thiopental (30 mg/kg), various cardiac-associated indices were measured, including right ventricle thickness, internal dimensions of the ventricle, thickness of interventricular septum, internal dimensions of the left ventricle (LV) during systole (LVESD) and diastole (LVEDD), and thickness of the posterior wall of left ventricular. Also, ejection fraction (EF) and shortening fraction (SF) of cardiac muscle were estimated [13].

Tissue sampling

Two days following the final training session and following overnight fasting, the animals were anesthetized by 50 IU Injection of ketamine into the peritoneal cavity (90 mg/kg) and xylazine (10 mg/kg). Thoracotomy was applied, and the heart tissue was dissected. Then, the left ventricle cardiac tissue was cut and stored in liquid nitrogen [14].

Genes expression assessment

In this study, the qRT-PCR technique was used for gene expression assessment. The mRNA samples of the left ventricular (50 mg) were extracted (RNA solution kit) and treated with DNase I. cDNA was made (Transe Criptor first strand cDNA synthesis kit, Germany), and qRT-PCR reactions were performed. The absorption ratio of 260/280 ng was 1-2.8 for all extracted samples. Electrophoresis and 1% agarose gel were used to check the quality of extracted RNA. Finally, gene expression levels were quantified using the Ct ($2^{-\Delta\Delta t}$) method (fold changes). The assessed genes were *mTORC1* (F: GAAGCCACAGCAGAAGAACC, R: ACGACCATGTTCTACCAGGC) [15], *Atg16* (F: GCCCAGTTGAGGATCAAACAC, R: CTGCTGCATTTGGTTGTTCAG) [16], *Atg7* (F: ATTGTGGCTCCTGCCCCAGT, R: GAGGACAGAGACCATCAGCTCCAC) [17], and *COLIII* (F: AGCTGGCCTTCCTC, R: GCTGTTTTTGCAG) [18].

Statistical analysis

The normality of the extracted data was assessed using the Shapiro-Wilk test. To identify group differences, one-way analysis of variance (ANOVA) and Tukey's post hoc test were used at a significance level of 0.05. Data analysis was applied using SPSS software, version 19, and the figures were drawn by Graph Pad Prism software, version 8 [19].

Results

Following the assessment of the total body weight, no significant ($P<0.05$) alteration was detected regarding

Table 1. The values of weight and echocardiographic indicators in different study groups

Variables	Mean±SD			
	Category	Control (n=8)	HIIT (n=8)	MICT (n=8)
Weight (g)	Before experiment	338±24	339±31	342±28
	After experiment	347±28	341±29	348±25
	P	0.08	0.09	0.07
Echocardiographic indices	LVEDD	7.8±0.4	4.8±0.2*	5.9±0.3*
	LVESD	4.5±0.5	2.8±0.1*	2.6±0.3*
	EF	59.3±5.7	79.1±5.6*	63.7±7.6*
	FS	29.1±4.7	43.7±3.6*	42.2±7.7#

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Abbreviations: HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; EF: Ejection fraction; FS: Fractional shortening.

*, #Significant differences compared to the control and HIIT groups.

the body weight among the treatments (MICT and HIIT) and control groups (Table 1). According to the findings, the gene expression of *mTORC1* was increased significantly (P<0.05) in HIIT and MICT groups compared to control animals. Also, HIIT showed significantly higher levels of *mTORC1* gene expression than the MICT group (P<0.05) (Figure 1A). The *Atg16* gene expression was significantly accelerated in HIIT and MICT groups compared to control animals (P<0.05). It was also found that the gene expression of MICT was accelerated significantly (P<0.05) compared to the HIIT group (Figure 1B). The gene expression of *Atg7* was increased significantly (P<0.05) in HIIT and MICT groups that control animals. Also, it was found that *Atg7* gene expression was significantly higher in the HIIT group than in the MICT group (P<0.05) (Figure 1C). The *COLIII* gene expression was significantly lower in the MICT and HIIT groups than in control animals (P<0.05). According to the findings, HIIT was not significantly higher compared to the MICT group (P>0.05) (Figure 1D). Since the figures represented, the LVEDD (Figure 2A) and LVESD (Figure 2B) were decreased significantly (P<0.05) in HIIT and MICT groups than control animals. Also, LVESD and LVEDD showed significantly lower levels in the MICT group than in the HIIT group (P<0.05). The EF (Figure 2C) and SF (Figure 2D) indicators were increased significantly in both groups of MICT and HIIT groups than in control animals (P<0.05). The HIIT group had significantly higher levels than the MICT group (P<0.05).

Discussion

The findings showed no body weight differences in the treatment groups compared to the control animals. Also, LVEDD and LVESD were decreased in the MICT and HIIT groups. Besides, the training accelerated EF and FS indices. These changes were highlighted in the HIIT group than in the MICT group. Gene expression assessment of *mTORC1, Atg16*, and *Atg7* also showed higher levels in the HIIT and MICT groups and lower levels in the *COLIII* gene. Aging is associated with changes in the cardiovascular system affecting cardiac function. Some of these changes are normal and occur with age, while others are due to modifiable factors and can lead to heart disease. The impact of aging on the cardiovascular system can be observed across molecular, cellular, tissue, organ, and systemic levels. Aging-related structural alterations affect the myocardium, cardiac conduction system, and endocardium. Age-related structural changes, particularly affecting the contractility of the left ventricular wall, have a significant impact. The heart's pumping efficiency decreases with age due to various factors. Aging notably affects both the heart and arteries, contributing to increased cardiovascular diseases such as atherosclerosis, hypertension, and heart failure. However, lifestyle factors, including physical activity, can influence the aging process of the heart and arteries, potentially slowing its progression in healthy individuals. Exercise training has been shown to have a positive effect on cardiac function. Regular physical activity reduces resting heart rate, blood pressure, and markers associated with atherosclerosis while promoting physiological cardiac hypertrophy.

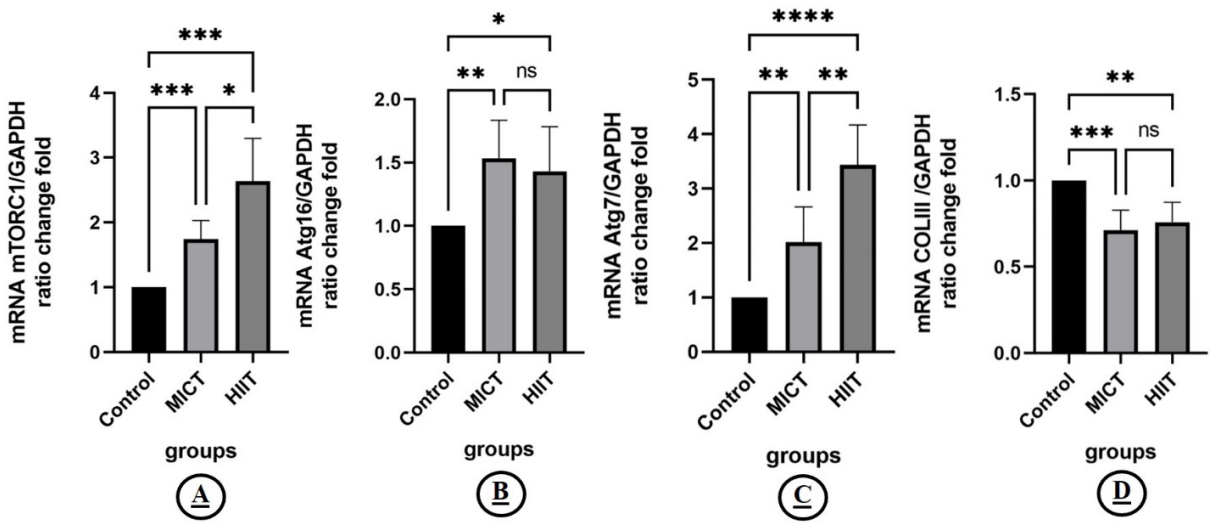

Figure 1. The findings for different study groups

A) *mTORC1* gene expression, B) *Atg16* gene expression, C) *Atg7* gene expression, D) *COLIII* gene expression

Abbreviations: HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; Ns: Not seen.

Notes: GAPDH is an internal control. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

Exercise enhances myocardial blood flow and raises high-density lipoprotein (HDL) cholesterol levels, collectively easing strain on the heart and improving cardiovascular function in both healthy individuals and those with medical conditions. A systematic review comprising 63 studies revealed that exercise-focused cardiac rehabilitation enhanced cardiovascular function. These studies encompassed diverse forms of aerobic exercise spanning various intensities and durations [20]. Research has demonstrated that the *mTORC1* genetic pathway is

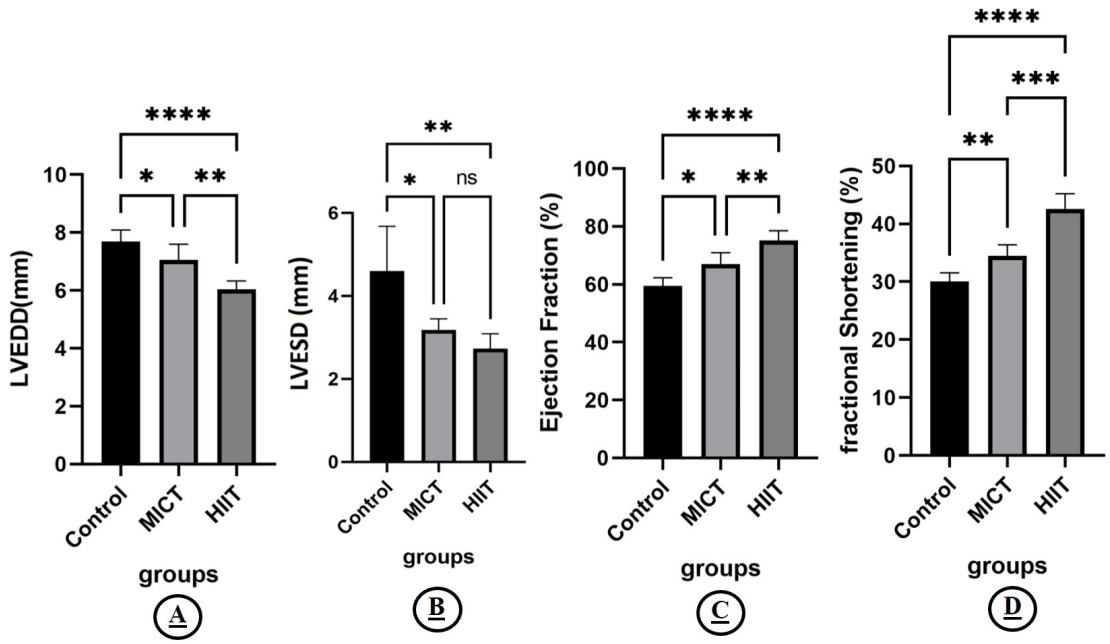

Figure 2. The results for different study groups

A) LVEDD, B) LVESD, C) EF, and D) FS

Abbreviations: HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; EF: Ejection fraction; FS: Fractional shortening.

*P<0.05, **P<0.01, ***P<0.00, ****P<0.0001.

involved in regulating cardiac function. Experiments using mTOR loss-of-function models have shown that activating *mTORC1* is essential for developing adaptive cardiac hypertrophy [21]. The mTOR pathway, particularly *mTORC1*, has been shown to control aging, lifespan, and healthspan by regulating cardiac function. It is widely recognized that *mTORC1* is crucial for stimulating protein synthesis, lipid metabolism, mitochondrial biogenesis, and nucleotide synthesis, and other cellular processes. In cardiac tissue, *mTORC1* has been shown to regulate protein synthesis and autophagy, which are important for maintaining cardiac function. Exercise training has been shown to activate the *mTORC1* genetic pathway, leading to increased protein synthesis and skeletal muscle mass. However, the effect of exercise training on the *mTORC1* pathway in cardiac tissue is less clear. Further research is needed to determine the impact of exercise training on the *mTORC1* pathway in cardiac tissue and its potential role in regulating cardiac function. Autophagy is a cellular mechanism essential for maintaining cellular balance by breaking down and recycling damaged organelles and proteins.

Exercise has been shown to affect autophagy gene expression, with some studies suggesting that HIIT and MICT can activate autophagy in skeletal muscle and other tissues [22-24]. However, the effect of HIIT and MICT on autophagy gene expression in cardiac tissue is less clear. Some studies suggest that HIIT can activate autophagy in the myocardium, while others suggest that HIIT can disable autophagy, apoptosis, and atrophy pathways [25, 26]. One study found that HIIT led to cellular process improvement by promoting autophagy, while another study found that HIIT inhibited autophagy [27]. The observed inconsistency in exercise effects could be due to the condition of examined subjects, the duration and intensity of the exercise, and the methods used to measure autophagy gene expression. Further research is needed to determine the effect of HIIT and MICT on autophagy gene expression in cardiac tissue and its potential role in regulating cardiac function. Collagen type III deposition in cardiac tissue is an important factor in the aging process and considerably affects cardiac function. Collagen type III deposition in cardiac tissue increases with age, leading to fibrosis and stiffening of the myocardium. Increased collagen deposition and fibrosis have been associated with stiffening of the myocardium, as well as dysfunction in both diastole and systole, and altered structure and function of the heart [28]. Collagen type I and collagen type III provide structural support for muscle cells and are critical for cardiac function. The production and breakdown of collagen, a key structural protein, are influenced by a complex interplay of biochemical mediators, ischemia, stretching, and other factors [29]. The cardiac extracellular matrix (ECM), primarily made up of fibrillar collagen, helps maintain myocardial integrity, facilitates force transmission, and is crucial for preserving cardiac structural integrity [30]. Collagen type III deposition in cardiac tissue can lead to fibrotic remodeling, which can contribute to the development of heart failure [31]. Understanding the role of collagen type III deposition in cardiac tissue in aging animals is important for developing treatments for age-related cardiac dysfunction. More investigation is required to understand how collagen type III is deposited in the heart tissue of older animals and how this affects their cardiac function.

The role of HIIT and MICT on cardiac function can be assessed using 2-dimensional echocardiography features such as LVEDD, LVESD, EF, and FS. A study on patients early after ST-segment elevation myocardial infarction (STEMI) found that HIIT was not different from isocaloric MICT with regard toregarding the short-term effects on LVEDVi and LVESVi [32]. There is limited evidence regarding the impact of HIIT on heart failure with preserved ejection fraction (HFpEF), as most studies examining HIIT in heart failure have predominantly concentrated on heart failure with reduced ejection fraction. (HFrEF) [33]. A meta-analysis of randomized controlled trials concluded that HIIT was superior to MICT in enhancing left ventricular ejection fraction (LVEF) among patients with coronary artery disease (CAD) [34]. Another study demonstrated that HIIT was more effective than MICT in enhancing physical performance and promoting cardiac and skeletal muscle adaptations in a rat model [24]. A randomized controlled trial found that an optimized HIIT protocol was significantly superior to classical interval training in improving heart rate variability in chronic heart failure patients [35]. The findings suggest that HIIT may positively affect cardiac function, particularly in improving LVEF and physical performance. However, more research is needed to determine the long-term effects of HIIT and MICT on cardiac function and their potential role in preventing or treating cardiovascular disease.

Conclusion

The results of the current study revealed that the training can effectively accelerate autophagy-associated gene expression and *mTORC1* molecular pathway. Also, collagen III deposition was a determining factor that decreased after cardiac tissue training. It seems that the cardiac function indicators, including LVEDD and

LVESD, decreased, while EF and FS increased, representing higher levels of cardiac output in old age. The findings of the current study suggest that HIIT is more effective for cardiac function and cardiac output than MICT. Thus, HIIT for older adults' heart seems to be a precise research topic in future studies.

Ethical Considerations

Compliance with ethical guidelines

All stages of animal manipulation and ethical issues were conducted according to the guidelines set forth by the Ethics Committee of Islamic Azad University (Ethic Code: IR.IAU.SRB.REC.1400.191).

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Authors' contributions

Conceptualization and Supervision: Mandana Gholami; Methodology: Mandana Gholami; Investigation, Writing – original draft, and Writing – review & editing: All authors; Data collection: Azadeh Taheri; Data analysis: Azadeh Taheri and Hossein Abednatanzi; Funding acquisition and Resources: Mandana Gholami, and Azadeh Taheri.

Conflict of interest

The authors declared no conflict of interest.

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